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COMPOSITION OF CEREBRAL FLUIDS IN GOATS ADAPTED TO HIGH ALTITUDE

Running head:

Cerebral fluids at high altitude

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The ionic composition of cerebral ISF was explored in 6 unanesthetized goats at sea level (SL) and again after 5 days at simulated high altitude (HA) of 4,300 m, by measuring net transependymal fluxes of HCO_3^-, Cl^- and lactate during ventriculo-cisternal perfusions with lactate-free artificial CSF with various [HCO_3^-] and [Cl^-]: concentration of an ion in cerebral ISF is indicated by concentration of that ion in the inflowing perfusate, that produces zero flux. Ventilatory acclimatization to HA was established (Pa_{CO_2} 41.3 and 34.3 torr at SL and HA, respectively, $p<0.001$), hyperventilation persisting during acute hyperoxia

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(Pa$_{O_2}$ >250 torr). Mean cisternal-CSF pH was more alkaline at HA (7.322 vs. 7.300 at SL, $p<0.001$). At SL, zero transependymal flux of HCO_3^- and Cl^- occurred when the ventriculo-cisternal system was perfused with fluids with [HCO_3^-] and [Cl^-] equal to those in the goat's own CSF. At HA, Cl^- flux again was zero when [Cl^-] in perfusate and in the goat's own CSF were equal; however, for HCO_3^-, zero flux occurred at HA when [HCO_3^-] in perfusate was significantly lower ($p<0.001$) than in CSF. Mean negative transependymal flux (washout) of lactate was 16 times larger at HA than at SL (-0.147 vs. -0.009 μM/min; $p<0.001$). We conclude that, at SL, [HCO_3^-] and [Cl^-] in CSF were the same as in cerebral ISF, which is in agreement with previously published findings. In goats adapted to HA, [Cl^-] in cerebral ISF remained equal to [Cl^-] in CSF, while [HCO_3^-] in cerebral ISF was demonstrably lower, and [lactate] presumably higher, than in CSF. The fluid surrounding the central chemoreceptors appears to be more acidic in goats acclimatized to HA than at SL, in spite of the alkalosis in cisternal CSF. This may contribute to ventilatory acclimatization to HA.

Abstract

The ionic composition of cerebral ISF was explored in 6 unanesthetized goats at sea level (SL) and again after 5 days at simulated high altitude (HA) of 4300 m, by measuring net transependymal fluxes of HCO_3^-, Cl^- and lactate during ventriculo-cisternal perfusions with lactate-free artificial CSF with various (HCO_3^-) and (Cl^-): concentration of an ion in cerebral ISF is indicated by concentration of that ion in the inflowing perfusate, that produces zero flux. Ventilatory acclimatization to HA was established (Pa_{CO_2} 41.3 and 34.3 torr at SL and HA, respectively, $p<0.001$), hyperventilation persisting during acute hyperoxia ($Pa_{O_2}>250$ torr). Mean cisternal-CSF pH was more alkaline at HA (7.322 vs. 7.300 at SL, $p<0.001$). At SL, zero transependymal flux of HCO_3^- and Cl^- occurred when the ventriculo-cisternal system was perfused with fluids with $[HCO_3^-]$ and $[Cl^-]$ equal to those in the goat's own CSF. At HA, Cl^- flux again was zero when $[Cl^-]$ in perfusate and in the goat's own CSF were equal; however, for HCO_3^-, zero flux occurred at HA when $[HCO_3^-]$ in perfusate was significantly lower ($p<0.001$) than in CSF. Mean negative transependymal flux (washout) of lactate was 16 times larger at HA than at SL (-0.147 vs. -0.009 μM/min; $p<0.001$). We conclude that, at SL, $[HCO_3^-]$ and $[Cl^-]$ in CSF were the same as in cerebral ISF, which is in agreement with previously published findings. In goats adapted to HA, $[Cl^-]$ in cerebral ISF remained equal to $[Cl^-]$ in CSF, while $[HCO_3^-]$ in cerebral ISF was demonstrably lower, and [lactate] presumably higher, than in CSF. The fluid surrounding the central chemoreceptors appears to be more acidic in goats acclimatized to HA than at SL, in spite of the alkalosis in cisternal CSF. This may contribute to ventilatory acclimatization to HA.

Key words:

CSF

cerebral interstitial fluid

regulation of respiration

ventriculo-cisternal perfusions

ionic fluxes between CSF and brain

INTRODUCTION

Mechanisms responsible for ventilatory adaptation to high altitude (HA) are still in dispute (14). In 1963, Severinghaus et al (26) attributed the progressive hyperventilation to correction of the initial CSF alkalosis, brought about by lowering CSF [HCO_3^-] through active transport of ions across the blood-brain barrier. This hypothesis, elegant in its simplicity, was later challenged by Dempsey and his colleagues. They found that CSF pH in humans (7,8,10) and ponies (19) was distinctly more alkaline after ventilatory adaptation to HA than at sea level (SL). Similar findings were subsequently obtained by Bureau and Bouverot in dogs (4) and by Weiskopf et al in humans (27). Recently, Crawford and Severinghaus (5) reinvestigated the ventilatory adaptation of humans to HA and concluded that the alkalosis seen in CSF was a reflection of the response of the peripheral chemoreceptors to hypoxemia, and of other ventilatory drives, including those from the central chemoreceptors responding to [H^+] (the latter affected by local CNS tissue P_{CO_2}, which can vary with accompanying changes in local blood flow).

From studies in animals at SL several authors have concluded that the "central chemoreceptors" are located in the cerebral ISF, at some distance from the surface of the medulla, and not simply exposed to the cisternal CSF (3,12,21). It is therefore possible that in acclimatization to HA, the medullary chemoreceptors are responding to a [H^+] that may not be the same as that reflected in [HCO_3^-] and P_{CO_2} of large-cavity CSF (14). Indeed, Davies (6) recently concluded that, in anesthetized dogs during three hours of hypoxia, the observed increase in ventilation correlated with increase in [H^+], which was estimated for cerebral ECF at a chemosensitive area assumed to be located at a certain distance along a gradient of [HCO_3^-] between CSF and blood.

The ionic composition of the cerebral ISF (including $[H^+]$) in animals at SL has been shown to be the same as that in the large-cavity CSF (9). However, there is no information on the composition of the cerebral ISF in animals acclimatized to HA. The experiments to be described were done to explore the relationship between the ionic composition of CSF and that of the cerebral ISF in unanesthetized goats adapted to a simulated altitude of 4300 m. By perfusing the ventriculo-cisternal system with artificial CSF of variable ionic composition, net transependymal fluxes (9,21) were derived for HCO_3^-, Cl^- and lactate. The results indicate that in goats acclimatized to HA, $[H^+]$ in the fluid surrounding the central chemoreceptors is different from that seen in the cisternal CSF and appears to be acidotic enough to account for the hyperventilation observed in the acclimatized animals.

Methods

1. General

Nylon guide tubes were permanently implanted over the lateral ventricles and cisternae magnae in 6 goats (mean body weight 40 kg, range 33-48 kg) following the techniques described by Pappenheimer et al (22); the animals were also provided with skin-denervated carotid loops. Three to six weeks were allowed for healing and post-operative recovery. Before each experiment, the cerebral cavities were punctured through the guide tubes using needles of adjustable length, and a plastic cannula was percutaneously inserted into the carotid artery, without anesthesia.

Measurements were made of resting ventilation and CO_2 production while the goats inhaled room air; an anaerobic sample of cisternal CSF was obtained. Respiratory measurements were then repeated with inhalation of 100% O_2. Subsequently, the ventriculo-cisternal system of the animals was perfused with sterile artificial CSF with various ionic compositions while the goats were breathing room air (see below). All measurements were made twice, once while the animals were adapted to normal barometric pressure (50 m above SL), and again at simulated high altitude, after 5 days' adaptation.

2. Simulated high altitude

A hypobaric chamber with round-the-clock monitoring of pressure, temperature, and composition of air was used. The pressure was kept at 446 torr (range ± 5 torr, corresponding to altitude of 4300 m), temperature at 21 ± 1 C, and air flow such that F_{CO_2} never exceeded 0.004. Lights were turned off at night. The goats moved freely in stalls similar to those in the regular animal quarters. They were fed regularly and had free access to water and

salt licks. The animals tolerated the 5-day stay in the chamber without any signs of discomfort.

3. Respiratory measurements

A latex rubber respiratory mask was snuggly fitted over the goat's snout. While wearing the mask, the animals appeared calm as they breathed air or O_2 through a low-resistance "triple J" valve having dead space 320 ml (Warren E. Collins, Inc.). During periods of breathing O_2, the inspired gas was supplied from a Douglas bag. Concentration of CO_2 in expired gases was measured with an LB-2 infrared analyzer (Beckman Instruments, Inc.) or an MGA-1100A mass spectrometer (Perkin-Elmer Corp.) calibrated with gases analyzed with a Scholander apparatus. Volume of expired gas was measured with a Wedge Spirometer (Med-Science Electronics, Inc.). Arterial blood was sampled and $\dot{V}_E$ and mixed-expired P_{CO_2} measured after a steady state in gas exchange had been reached, as judged by stability of the continuously-monitored mixed-expired P_{CO_2} and PET_{CO_2}. $\dot{V}_A$ was calculated using Enghoff's modification of Bohr's formula for respiratory dead space.

4. Ventriculo-cisternal perfusions

The technique described by Pappenheimer et al (11,21,22) was applied. Ventricular inflow was controlled at 1.5 - 2.0 ml/min with a constant-flow infusion pump calibrated for each experimental day. The tip of the cisternal outflow tubing was kept at the level of the goat's external auditory meatus, the fluid collected aerobically in glass cylinders; volume was determined by weighing. Inflow pressures, recorded at the hub of the needle for ventricular inflow, and continuously monitored, were usually 3-4 cm H_2O higher than the pressure at the tip of the outflow tubing.

During each experimental day, perfusions were done with three fluids. One approximated the ionic composition of cisternal fluid of normal goats (22); it contained the following constituents (in mM/L): Na 150, K 2.8, Ca 1.3, Mg 0.8, Cl 128, HCO_3 22, inorganic P 0.5. The other two fluids differed in the concentration of HCO_3, being 7-8 mM/L lower or higher than normal (about 15 and 28 mM/L, respectively) with complementary changes in [Cl]. Sterile solutions were prepared as described by Pappenheimer et al (11,22). To avoid precipitation of Ca and Mg carbonates, 5% CO_2 (balance O_2) was bubbled through the solutions for at least 1 hour before Ca and Mg salts were added. Osmolarity, measured with a model 2001 osmometer (Precision System), was adjusted to 300 mOsm/L by adding sterile pyrogen-free water or 5% NaCl. Approximately 1 nanocurie of ^{3}H-inulin, specific activity 160 m Curie/g (New England Nuclear), was added per 1 ml of perfusion fluid. Prior to infusion, the fluids were passed through sterile Millipore filters, pore size 0.22 μm (Millipore Corp.).

Before collecting fluids for analysis, each of the three different fluids was perfused through the goat's ventriculo-cisternal system until at least 75 ml of outflow was collected, which is about three times the volume needed to establish steady-state distribution of substances when the CSF system of goats is perfused (11). Outflow fluids were collected for analysis over 15 to 20 minutes. Most perfusions of a given composition were carried out twice, with sampling of arterial blood between the two collection periods.

Net transependymal fluxes of HCO_3^-, Cl^- and lactate were calculated using equations derived by Pappenheimer et al (9,11,21,22):

$$\dot{n} = \dot{V}_i (c_i - c_f) - (\dot{V}_o + C_{In}) (c_o - c_f),$$

where $\dot{n}$ = net flux of the ion (μM/min) between the perfusate and the cerebral ISF,

$\dot{V}$ = rate of flow of perfusion fluids (ml/min),

c = concentration of the ion (mM/kg H_2O),

i,o,f,p = subscripts referring respectively to inflow, outflow, freshly formed CSF and arterial plasma; f taken as equal to p (9),

C_{In} = clearance of inulin from ventricular system $(\dot{V}_i c_i - \dot{V}_o c_o)/c_o$ (ml/min) (11).

The flux thus calculated is corrected both for the entry of the ion under consideration via bulk formation of CSF at the choroid plexus, and for exit of the ion via bulk reabsorption of CSF in arachnoid villi. Therefore, the transependymal flux of an ion represents the net passive exchange between the ventriculo-cisternal perfusate and the cerebral ISF, across the leaky ependyma in the ventricles and pia-glia on the cerebral surface. When transependymal flux of an ion is zero, the concentration of that ion in the inflowing perfusate indicates its concentration in the cerebral ISF (9).

5. Analytical techniques

P_{CO_2}, P_{O_2} and pH in arterial blood and in CSF were measured at 37 C with standard P_{CO_2} and P_{O_2} electrodes (Radiometer A/S) and a Severinghaus pH electrode (23), using Radiometer electronics (model PHM 72 MK2). Corrections were made for body temperature (17,24). Precision buffers (Radiometer) and gases analyzed with Scholander apparatus for CO_2 and O_2 were used to calibrate the electrodes. CO_2 concentration (C_{CO_2}) in CSF and in perfusion fluids was measured with the Natelson Microgasometer (Scientific Industries, Inc.). Samples of cisternal outflows, collected aerobically, were equilibrated for at least 25 minutes in a tonometer at 37 C with gas containing 5.5% CO_2. Samples were

subsequently handled anaerobically while being analyzed for pH and C_{CO_2}. Bicarbonate concentrations in blood plasma, CSF, and perfusates were calculated from measured pH and P_{CO_2}, or C_{CO_2} using published balues for pK' and CO_2 solubilities (17,24). Chloride in CSF, in perfusion fluids, and in anaerobically separated blood plasma was determined by potentiometric titration (Aminco-Cotlove, American Instrument Co.). Lactate was determined in whole blood, CSF, and perfusion fluids with an enzymatic technique (Sigma Chemical Co.). Concentration of ^{3}H-inulin in perfusion fluids was measured with a three-channel Packard Tricarb Liquid Scintillation Spectrometer, Model 3385 (Packard Instruments Co.). A 0.5 ml sample was mixed with 10 ml of Beckman Ready-solv GP solution (Beckman Instruments). Quenching was corrected for by means of an external standard. Efficiency for tritium counting was 60 percent.

When calculating transependymal fluxes, concentrations of HCO_3^- and Cl^-, determined as mM/L of plasma, were converted to molality (mM/kg H_2O) by dividing by 0.93 (9). Lactate, determined in mM/L of whole blood, was converted to molality (mM/kg H_2O in whole blood) by dividing by 0.804 (2). Following Huckabee's recommendations (13) we assumed that lactate was evenly distributed between RBC and plasma water. In CSF and in the protein-free perfusion fluids, concentrations in mM/L were applied in calculations of fluxes; correcting for molality was deemed insignificant.

6. Statistical analyses

Statistical significance was determined by the Student t-test for paired samples, or by independent t-test, as applicable. Linear regression analysis was performed with evaluation of parameters of the lines by F-test (1).

Results

1. Respiratory adaptation to simulated high altitude

Table 1 summarizes respiratory data obtained in the goats at SL and after 5 days at simulated HA. Mean $\dot{V}_{CO_2}$ did not change appreciably. Mean resting $\dot{V}_A$, during air breathing, increased with acclimatization from a sea-level value of 2.9 to 3.9 l/min., BTPS ($p<0.001$); concomitantly, mean Pa_{CO_2} decreased from 41.3 to 34.3 torr ($p<0.001$). The hyperventilation at HA persisted during acute hyperoxia (Pa_{O_2} > 250 torr): $\dot{V}_A$ was higher, and Pa_{CO_2} lower, after 5 days at HA, than at SL (4.0 and 3.1 l/min., BTPS, $p<0.02$; 38.5 and 42.6 torr, $p<0.02$).

Data on arterial blood sampled while the goats were quietly breathing room air are presented in Table 2. Pa_{O_2}, as expected, was reduced from its mean value of 104.4 torr at SL to 42.6 torr after 5 days at simulated HA ($p<0.001$). $[HCO_3^-]$ in plasma decreased from the mean sea-level value of 29.1 mM/L to 23.2 mM/L ($p<0.02$). Mean $[Cl^-]$ in plasma increased from 105.9 to 111.5 mM/l ($p<0.01$). Concentration of lactate in whole blood was 0.6 mM/L at SL and 1.2 mM/L at HA (a statistically insignificant difference). These changes in the ionic composition of arterial blood, together with the observed decrease in Pa_{CO_2}, resulted in a small increase in arterial-blood pH of about 0.01 units at HA, which was not statistically significant.

2. Composition of CSF (Table 3)

There was a statistically significant alkaline shift in the goats' cisternal CSF after 5 days at PB ~446 torr: mean pH increased from 7.300 at SL to 7.322 at HA ($p<0.001$), in spite of a significant increase in CSF $[Cl^-]$ and [Lactate], and a decrease in $[HCO_3^-]$. The mean change in CSF

$[HCO_3^-]$ was -3.8 ± 0.5 mM/L (±S.E.); this was stoichiometrically matched by a mean combined change in [Cl] + [Lactate] of + 3.6 ± 0.4 mM/L. The alkaline shift in cisternal CSF was thus produced by a marked decrease in P_{CO_2}, from 47.2 torr at SL to 38.9 torr at HA ($p<0.001$).

3. Transependymal fluxes of ions

In 6 goats, complete sets of data needed for computation of transependymal fluxes for HCO_3^- were obtained 25 times at SL and 22 times at HA; for Cl^-, 24 times at SL and 17 times at HA. For lactate, data were obtained in only 4 goats, 17 times both at SL and HA. Detailed data are available from tables deposited with the National Auxiliary Publications Service of ASIS.

Figures 1 and 2 show net transependymal fluxes of HCO_3^- and Cl^- plotted against the differences in the concentrations of these ions between the various ventricular inflows and the goat's own CSF ($\Delta[HCO_3^-]$ and $\Delta[Cl^-]$); if this difference equals zero, the concentration of the ion in the fluid entering the ventricles is equal to that in the goat's own CSF. Arbitrarily, positive flux means uptake of the ion from the perfusate into cerebral ISF; negative flux means washout of the ion from cerebral ISF into the perfusate.

When the concentration of Cl^- or HCO_3^- in the perfusate exceeded that in the goat's own CSF, the flux of the ion was positive, i.e. into the brain. The dashed and full-drawn lines represent least-square linear regressions derived from the data at SL and at HA, respectively. Parameters for these regression lines are given in Table 4. The y-intercepts (a) are statistically indistinguishable from zero for HCO_3^- fluxes at SL, and for Cl^- fluxes at both SL and HA. However, for the transependymal flux of HCO_3^- at HA, this intercept is significantly different from zero ($p<0.001$). Thus, in goats at SL, when the

concentration of HCO_3^- or of Cl^- in the inflowing perfusate equals that in the goat's CSF ($\Delta[Cl^-] = 0$, $\Delta[HCO_3^-] = 0$, Figures 1 and 2), transependymal flux is also zero. However, in our goats adapted to HA, there was a significantly positive transependymal flux of HCO_3^- (2.58 ± 0.28 μM/min, $p<0.001$) when $\Delta[HCO_3^-]$ equalled zero (Figure 1, Table 4). The condition for zero flux of HCO_3^- was fulfilled only when $[HCO_3^-]$ in the inflowing perfusate was significantly ($p<0.001$) lower than $[HCO_3^-]$ in the goat's own CSF; the estimate of the x-intercept is -6.1 mM/L (-4.1 and -3.6 mM/L being the upper 95 and 99% tolerance limits, respectively, for $\underset{\cdot}{x}$ at $y = 0$).

All perfusion fluids were prepared free of lactate; therefore, analysis of the calculated transependymal fluxes for lactate, analogous to that shown in Figures 1 and 2 for HCO_3^- and Cl^-, was not possible. Lactate flux could be calculated, however, by setting the inflow concentration equal to zero (see Methods). The transependymal flux of lactate did not vary systematically while the ventriculo-cisternal system was being perfused with solutions of various $[HCO_3^-]$ and $[Cl^-]$ at SL or HA. The mean (±S.E.) of all lactate fluxes measured at SL was -0.09 ± 0.04 μM/min which was significantly different from zero ($p<0.05$); after adaptation to HA the mean transependymal washout of lactate (-1.47 ± 0.17 μM/min) was significantly larger ($p<0.001$).

Discussion

Our data show that ventilatory acclimatization to HA was established in the goats after 5 days at P_B ~446 torr, findings analogous to those of Mines and Sørensen (16), Lahiri et al (15), and Morrill and Kellogg (18), in this species. In the arterial blood, hypoxic hypocapnia prevailed, with almost complete renal compensation of the respiratory alkalosis. In the cisternal CSF, however, pH was distinctly more alkaline at HA than at SL. This is similar to findings in ponies (19), dogs (4), and humans either in lumbar (5,7,8, 10,27) or cisternal (27) CSF.

The mean difference (±S.E.) in P_{CO_2} between CSF and arterial blood was reduced from the sea-level value of 6.1 ± 0.6 torr to 3.6 ± 1.1 at HA ($p<0.001$). This does not necessarily indicate an increase in cerebral blood flow (CBF) at HA because the blood CO_2 dissociation curve is steeper at lower values of P_{CO_2} (5). Crawford and Severinghaus (5) expressed the CSF-to-arterial gradient in P_{CO_2} as a ratio, CSF P_{CO_2}/Pa_{CO_2}, to circumvent the nonlinearity of the blood dissociation curve. They interpreted changes in this ratio to indicate reciprocal changes in CBF, assuming that the CSF-to-arterial P_{CO_2} ratio remains proportional to the cerebral venous-to-arterial P_{CO_2} ratio (and that the cerebral CO_2 production does not change markedly). In our observations, the mean (±S.E.) values of CSF P_{CO_2}/Pa_{CO_2} were 1.149 ± 0.018 at SL, and 1.102 ± 0.038 after 5 days at HA, a change suggesting increase in CBF (statistically insignificant). If the above assumptions apply to our goats, we would conclude that, in spite of the low Pa_{CO_2}, CBF was not lowered after adaptation to HA, and it might even have increased somewhat, a conclusion similar to the findings in human sojourners at HA (25), and in rats after 24 hours of hypoxic hypocapnia (20).

The ventriculo-cisternal perfusions with artificial CSF of variable [HCO_3^-]

and [Cl^-] were performed to establish the relation between the concentrations of these ions in CSF and in the cerebral ISF. Net transependymal fluxes, corrected both for entry of an ion by bulk formation of CSF and for exit of the ion by bulk absorption of CSF in choroid villi, represent passive exchange across the leaky ependyma in the ventricles and across the pia-glia on the cerebral surface (9,11,21). When there is a concentration gradient for an ion between the cerebral ISF and the fluid perfusing the large cavities, there is a measurable transependymal flux; if net flux is zero, there is no such concentration gradient. Therefore, when there is zero transependymal flux, the concentration of the ion under consideration in the inflow perfusate indicates the concentration of that ion in the cerebral ISF (9).

We found zero net transependymal flux of HCO_3^- and Cl^- when the ventriculocisternal system of goats at SL was perfused with fluids having concentrations of these ions equal to those in the goat's own CSF ($\Delta[HCO_3^-]$ and $\Delta[Cl^-]$ equal to zero, Figures 1 and 2). Therefore, we conclude that at SL, [HCO_3^-] and [Cl^-] in CSF were the same as in the cerebral ISF. This is in agreement with previous findings in goats at SL, either in normal acid-base balance or in steady acid-base disturbances of non-respiratory origin (9). After acclimatization to HA, net transependymal flux of Cl^- again was zero when [Cl^-] in the perfusion fluid equalled that in the CSF of acclimatized goats. Thus, we conclude that in goats adapted to HA, [Cl^-] in CSF remained equal to [Cl^-] in cerebral ISF. In contrast, HCO_3^- flux was significantly positive (flux into the brain tissue) when the perfusate had the same [HCO_3^-] as that in the goats own CSF ($\Delta[HCO_3^-] = 0$, Figure 1). For a positive net transependymal flux of HCO_3^- to occur, a gradient of [HCO_3^-] had to exist, with a lower concentration in the brain tissue than in the perfusate. For zero flux of HCO_3^- to occur in goats acclimatized to HA,

$[HCO_3^-]$ in the perfusate had to be lower than in CSF sampled from that goat. We therefore conclude that in goats adapted to HA, $[HCO_3^-]$ in cerebral ISF was demonstrably lower than in CSF.

These findings suggest that in goats adapted to HA, there exists a steady-state concentration gradient of $[HCO_3^-]$, and not of $[Cl^-]$, between CSF and cerebral ISF, across the leaky ependyma and pia glia, with a lower $[HCO_3^-]$ in cerebral ISF than in CSF. This may be, at least in part, owing to a concentration gradient of lactate going in the opposite direction. The latter notion is corroborated by the finding that the mean negative transependymal flux of lactate (washout of lactate), measured in 4 of our goats, was more than 16 times greater at HA than at SL.

From animal experiments involving respiratory measurements during ventriculocisternal perfusions with fluids of abnormal ionic composition (3,12,21), it has been concluded that the "central chemoreceptors" are located in the cerebral ISF, at some distance from the surface of the medulla. In cats, this distance was estimated by Berndt et al to be 200-400 μm (3). In goats with the ventriculocisternal system perfused with artificial CSF of abnormal $[HCO_3^-]$, the location of the central chemoreceptors was estimated by Pappenheimer et al (21) to be 3/4 along the concentration gradient of HCO_3^- between the fluid present in cisterna magna and that ascribed to the cerebral extracellular space. If we apply this model to our data, then $[HCO_3^-]$ in the fluid surrounding the central chemoreceptors in goats acclimatized to HA would be 3/4 the distance along the gradient between $[HCO_3^-]$ in cisternal CSF (19.6 mM/L, Table 3) and that assigned to the cerebral ISF (19.6 - 6.1 = 13.5 mM/L, Figure 1). Taking the mean CSF P_{CO_2} (Table 3) as a measure of the prevailing cerebral-tissue P_{CO_2}, pH in the fluid surrounding the medullary chemoreceptors (pH_r) would be equal to $6.13 + \log [(0.75 \times 13.5$

+ 0.25 x 19.6)/0.031 x 38.9] = 7.23. If a cerebral-ISF [HCO_3^-] corresponding to the upper 95% tolerance limit (cisternal [HCO_3^-] minus 4.1 mM/L), as predicted from data in Figure 1 and Table 4, were taken for this estimate of pH_r, the value would be 7.27. Both these estimates give pH values acidotic compared to SL, where pH in the fluid surrounding the central chemoreceptors should be equal to that measured in cisternal CSF, 7.30 (Table 3), since at SL, no gradient for [HCO_3^-] was found between CSF and ISF in the present or previous (9) experiments.

We conclude that the fluid surrounding the "central chemoreceptors" is more acidic in goats acclimatized to HA, than at SL, in spite of the alkalosis in cisternal CSF. This may contribute to the ventilatory acclimatization of the animals. This conclusion is similar to that of Davies (6), although it is derived from a different experimental approach, and is based on less indirect assumptions. Our conclusions are also compatible, at least in part, with those of Crawford and Severinghaus (5), which state that ventilatory drives other than those from peripheral chemoreceptors or those ascribed to the effect of [H^+] in bulk CSF are contributing to ventilatory acclimatization to HA.

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In conducting the research described in this report, the investigators adhered to the 'Guide for the Care and Use of Laboratory Animals,' as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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TABLE 1

RESPIRATORY ADAPTATION OF GOATS AFTER 5 DAYS AT SIMULATED HIGH ALTITUDE (4300m).

Means ± S.E.

F_{IO_2}	0.21		1.0	
	n=6		n=5	
	Sea Level	High Altitude	Sea Level	High Altitude
$\dot{V}_{CO_2}$ ml/min. STPD	151 ± 14	152 ± 10	164 ± 19	169 ± 10
	N.S.		N.S.	
$\dot{V}_A$ L/min. BTPS	2.9 ± 0.1	3.9 ± 0.2	3.1 ± 0.2	4.0 ± 0.4
	$p<0.001$		$p<0.02$	
Pa_{CO_2} torr	41.3 ± 1.3	34.3 ± 1.2	42.6 ± 2.0	38.3 ± 1.1
	$p<0.001$		$p<0.02$	

TABLE 2

ARTERIAL BLOOD AT SEA LEVEL AND AFTER 5 DAYS AT SIMULATED HIGH ALTITUDE (4300 m)

Data on 6 goats breathing room air — Means ± SE

	Sea Level	High Altitude	Statistical Significance§
P_{O_2}, torr	104.4 ± 2.5	42.6 ± 2.3	$p<0.001$
P_{CO_2}, torr	41.3 ± 1.3	34.3 ± 1.2	$p<0.001$
pH	7.438 ± 0.015	7.449 ± 0.015	N.S.
$[HCO_3^-]$, mM/L plasma	29.1 ± 1.4	23.2 ± 0.5	$p<0.02$
$[Cl^-]$, mM/L plasma	105.9 ± 1.0	111.5 ± 0.5	$p<0.01$
[Lactate], mM/L whole blood	0.6 ± 0.1*	1.2 ± 0.2#	N.S.†

* data on 3 goats

\# data on 4 goats

§ t-test for paired samples

† t-test for means of unpaired samples

TABLE 3

CISTERNAL CSF AT SEA LEVEL AND AFTER 5 DAYS AT SIMULATED HIGH ALTITUDE (4300 m)

Data on 6 goats breathing room air — Means ± S.E.

	Sea Level	High Altitude	Statistical Significance#
pH	7.300 ± .009	7.322 ± .006	$p<0.001$
P_{CO_2} torr	47.2 ± 1.2	38.9 ± 1.1	$p<0.001$
$[HCO_3^-]$ mM/L	23.3 ± 0.5	19.6 ± 0.4	$p<0.001$
$[Cl^-]$ mM/L	128.4 ± 0.6	130.3 ± 0.5	$p<0.02$
[Lactate]* mM/L	2.9 ± 0.1	4.2 ± 0.1	$p<0.001$

* data on 4 goats

\# t-test for paired samples

Table 4

Parameters (±S.E.) of regression lines relating net transependymal fluxes of ions (HCO_3^- and Cl^-) to the concentration of the ion in the inflow perfusate (c_i) and that in the goat's CSF (c_{csf}). Data shown in Figures 1 and 2.

Net ion flux = $a + b(c_i - c_{csf})$

	n	Intercept (mM/kg H_2O) (a)	Slope (ml/min) (b)	Correlation coefficient (r)
HCO_3^- flux				
Sea level	25	0.22 ± 0.11*	0.37 ± 0.02	0.96
High altitude	22	2.58 ± 0.28†	0.42 ± 0.05	0.90
Cl^- flux				
Sea level	24	-0.10 ± 0.22*	0.36 ± 0.03	0.94
High altitude	17	-0.14 ± 0.23*	0.40 ± 0.04	0.92

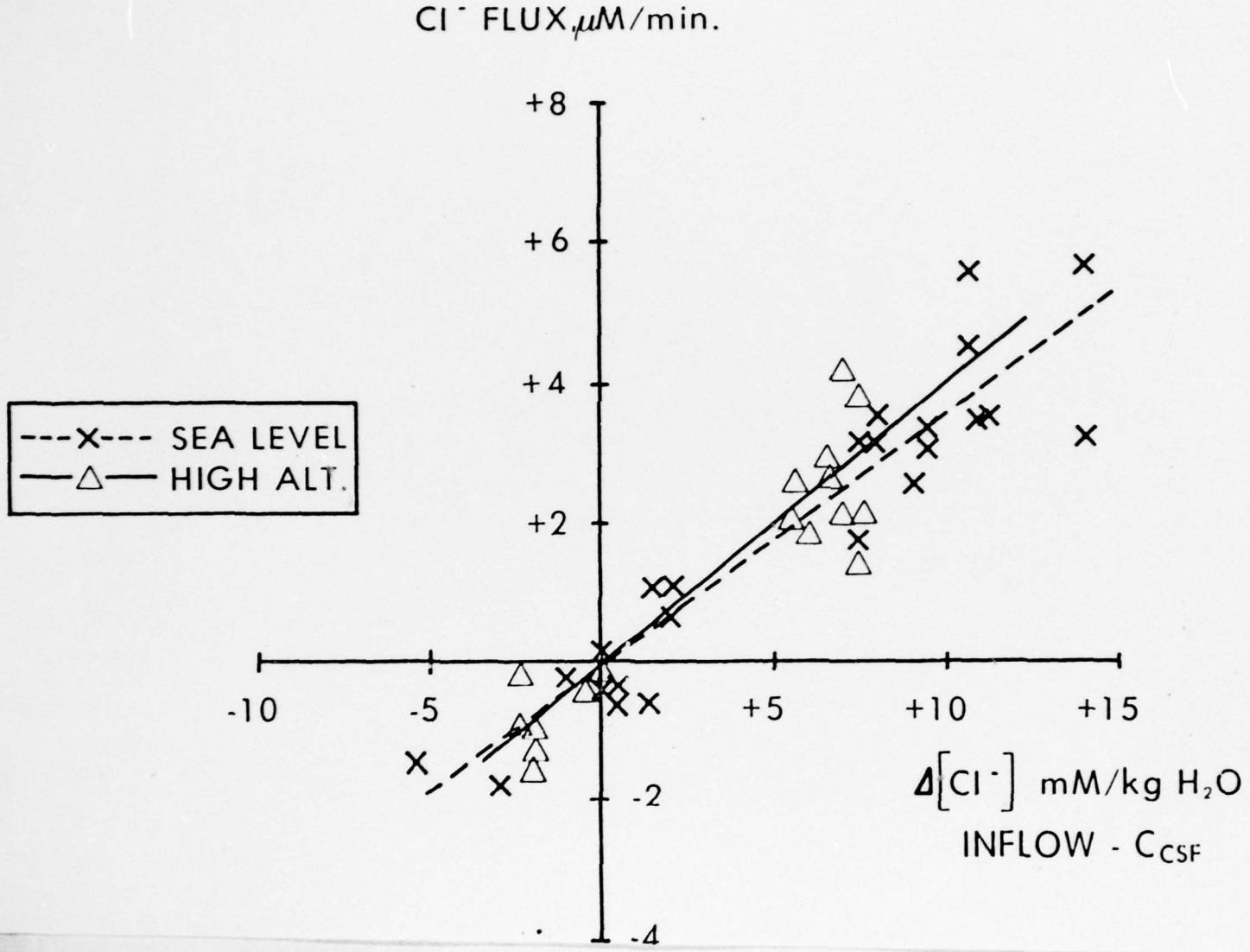
* Statistically indistinguishable from zero.

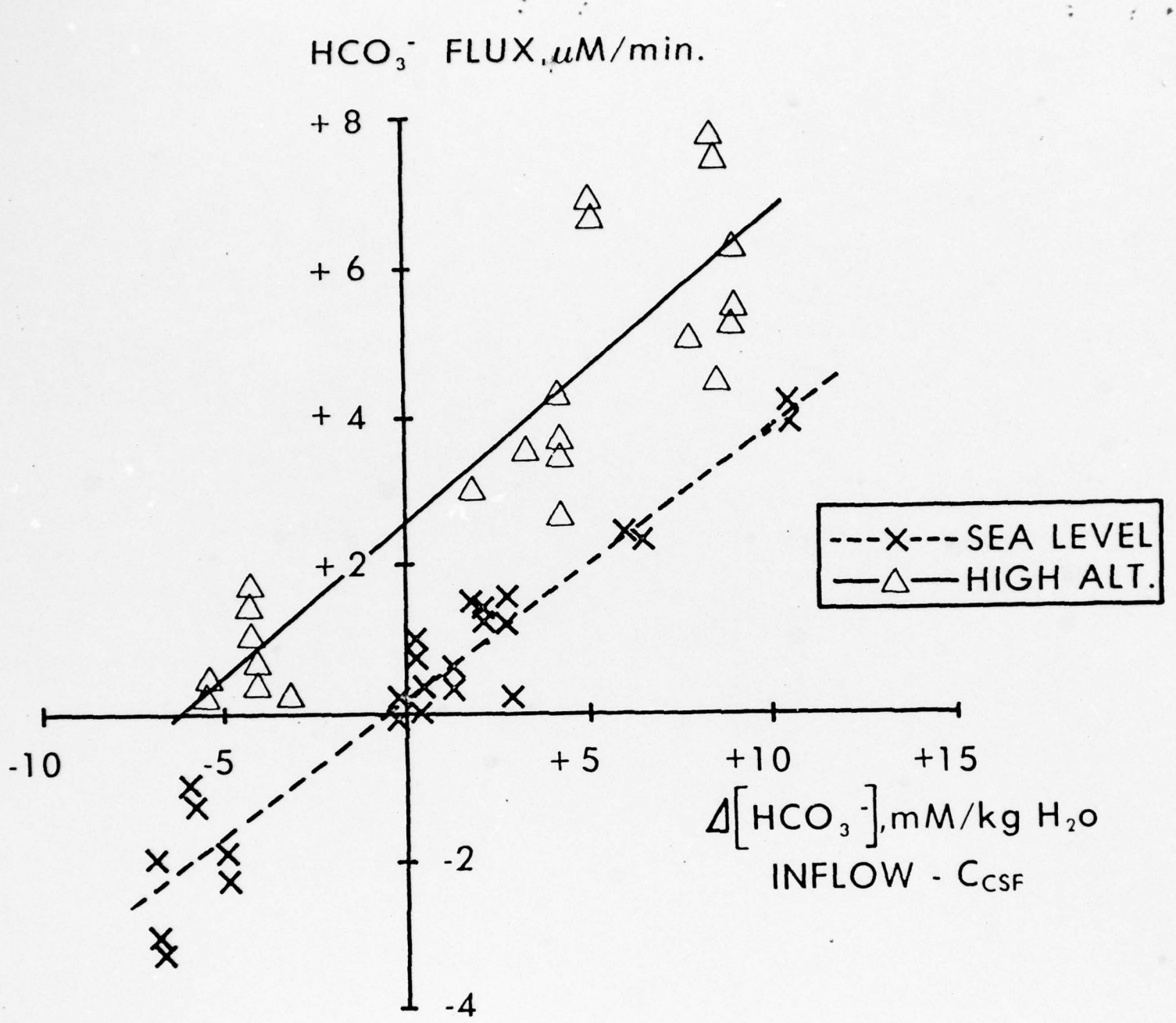
† Significantly different from zero ($p<0.001$; F-test). Value of x at y = 0 is -6.1 mM/kg H_2O, with upper 95% tolerance limit of -4.1 mM/kg H_2O.

Legends to Figures

Figure 1 — Net transependymal fluxes of HCO_3^- in goats adapted to sea level and to high altitude. Fluxes are plotted against the bicarbonate concentration difference between the inflowing perfusate, and the goat's CSF under the two conditions of respiratory adaptation. The straight lines are least-squares linear regressions; see Table 4 for paramaters of the regression lines.

Figure 2 — Net transependymal fluxes of Cl^- in goats adapted to sea level and high altitude. The plots are analogous to those for HCO_3^- fluxes shown in Figure 1.


Cl⁻ FLUX, μM/min.
+8
+6
+4
+2
-2
-4
-10
-5
+5
+10
+15
SEA LEVEL
HIGH ALT.
Δ[Cl⁻] mM/kg H₂O
INFLOW - C_CSF


HCO_3^- FLUX, μM/min.
+8
+6
+4
+2
-2
-4
-10
-5
+5
+10
+15
---X--- SEA LEVEL
—△— HIGH ALT.
$\Delta[HCO_3^-]$, mM/kg H_2O
INFLOW - C_{CSF}

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SEA LEVEL

Goat	Collection Period min:sec	$\dot{V}_i$ ml/min	$\dot{V}_o$ ml/min	$[HCO_3^-]$, mM/L c_i	c_o	c_p	cist CSF	$[Cl^-]$, mM/L c_i	c_o	c_p	cist CSF	[Lactate], mM/L c_o	c whole blood	cist CSF	Inulin cpm/ml c_i	c_o	C_{In} ml/min	HCO_3^- c_i-c_{csf} mM/kg H_2O	c_p mM/kg H_2O	Flux µM min	Cl^- c_i-c_{csf} mM/L	c_p mM/kg H_2O	Flux µM min	Lactate c_p mM/kg H_2O	Flux µM min
RU	15:35	2.017	1.932	24.0	24.3	27.5	24.4	136.5	133	108.5	129	0.76	0.60	2.61	870	780	0.319	+0.4	29.5	+0.6	+7.5	116.7	+3.2	0.75	+0.02
	15:12	2.017	2.342	24.0	24.5			136.5	132			0.77			870	758	0.150	+0.4	29.5	+0.1	+7.5	116.7	+1.8	0.75	+0.04
	15:11	2.017	2.106	17.5	19.2	27.5		140	136	108.5		0.73	0.60		882	831	0.034	-6.9	29.5	-3.4	+14.0	116.7	+5.7	0.75	-0.04
	15:07	2.017	2.107	17.5	19.1			140	137			0.72			882	824	0.051	-6.9	29.5	-3.1	+14.0	116.7	+3.2	0.75	-0.06
	15:10	2.017	2.255	27.1	26.8	26.8		-	-	-		0.76	0.63		911	837	0.061	+2.7	28.8	+1.2	-	-	-	0.78	-0.05
	19:07	2.017	2.171	27.1	26.7			-	-	-		-			911	756	0.259	+2.7	28.8	+1.6	-	-	-	0.78	-
AC	15:19	1.738	1.914	25.7	25.1	25.0	23.7	127	126	107	127.4	0.83	0.64	2.97	932	830	0.038	+2.0	26.9	+1.4	+0.4	115.0	-0.6	0.80	+0.05
	15:15	1.738	2.007	25.7	25.3			127	125			0.94			932	762	0.119	+2.0	26.9	+1.3	+0.4	115.0	-0.4	0.80	+0.08
	15:19	1.738	1.876	17.7	19.5	22.4		138	133	107		0.73	0.70		924	840	0.036	-5.0	24.1	-2.3	+10.6	115.0	+5.6	0.875	-0.26
	15:17	1.738	2.053	17.7	19.7			138	132			0.80			924	842	0.030	-5.0	24.1	-1.9	+10.6	115.0	+4.5	0.875	-0.16
	15:11	1.738	1.831	29.3	-	22.7		122	122	107		0.87	-		898	808	0.100	+6.0	24.4	+2.4	-5.4	115.0	-1.4	0.80	-
	15:15	1.738	1.865	29.3	27.2			122	-			0.85			898	798	0.095	+6.0	24.4	-	-5.4	115.0	-	0.80	+0.09
NU	15:11	1.733	1.888	25.2	27.0	26.7	25.0	128	124	102	126.6	0.77	0.50	3.03	551	446	0.252	+0.2	28.7	+0.8	+1.4	109.7	+1.1	0.63	-0.29
	15:08	1.733	2.054	25.2	25.5			128	125			0.79			551	452	0.055	+0.2	28.7	+0.9	+1.4	109.7	-0.6	0.63	-0.33
	15:03	1.733	1.923	18.2	-	26.7		136	131	102		-	0.60		511	444	0.072	-6.8	28.7	-	+9.4	109.7	+3.1	0.75	-
	15:16	1.733	2.001	18.2	-			136	133.5			-			511	422	0.098	-6.8	28.7	-	+9.4	109.7	+3.4	0.75	-
	15:12	1.733	1.872	35.5	30.8	25.2		118	-	103		-	0.80		544	419	0.377	+10.5	27.0	+3.9	-8.6	110.8	-	1.00	-
	15:15	1.733	1.957	35.5	30.7			118	-			1.02			544	420	0.287	+10.5	27.0	+4.2	-8.6	110.8	-	1.00	-0.04
SO	15:09	2.047	1.960	22.7	22.7	25.5	22.8	130	129	105	130	1.04	0.80	2.89	807	752	0.236	-0.1	27.4	0.0	0.0	112.9	-0.4	1.00	+0.08
	15:09	2.047	2.023	22.7	22.6			130	128.5			-			807	735	0.224	-0.1	27.4	+0.1	0.0	112.9	0.0	1.00	-
	15:05	2.047	2.017	16.8	-	23.9		141	138.5	105		0.96	0.80		742	720	0.092	-6.0	25.7	-	+11.0	112.9	+3.5	1.00	-0.08
	15:48	2.047	2.035	16.8	-			141	138.5			0.98			742	720	0.094	-6.0	25.7	-	+11.0	112.9	+3.5	1.00	-0.04
	14:57	2.047	2.088	25.7	25.6	23.8		127	127.5	106		-	0.80		752	734	0.009	+2.9	25.6	+0.2	-3.0	114.0	-1.7	1.00	-
	15:14	2.047	2.075	-	-			127	-			0.75			752	737	0.013	+2.9	25.6	-	-3.0	114.0	-	1.00	-0.52
TU	15:07	0.745	0.733	24.1	-	25.1	22.5	130	128	109	129				896	743	0.166	+1.9	27.0	-	-1.0	117.2	-0.2		
	15:20	0.745	0.877	24.4	23.1			130	-						896	757	0.005	+1.9	27.0	+1.5	-1.0	117.2	-		
	15:04	0.745	-	15.5	-	23.9		138	-	110					841	708	-	-7.0	25.7	-	+9.0	118.3	-		
	15:23	0.745	0.753	15.5	19.1			138	135						841	723	0.114	-7.0	25.7	-1.9	+9.0	118.3	+2.5		
	15:42	0.745	0.768	29.7	-	25.6		125	-	111					790	708	0.064	+7.2	27.5	-	-4.0	119.3	-		
	14:40	0.745	0.709	29.7	-			125	-						790	710	0.120	+7.2	27.5	-	-4.0	119.3	-		
LI	15:03	2.030	2.030	22.9	22.8	26.5	21.7	131	130	108	129				1545	1494	0.070	+1.2	28.5	+0.6	+2.0	116.0	+0.7		
	15:07	2.030	2.028	22.9	22.8			131	130						1545	1509	0.050	+1.2	28.5	+0.4	+2.0	116.0	+1.1		
	15:17	2.030	2.025	15.7	17.0	25.3		137	134	107					1665	1544	0.164	-6.0	27.2	-1.0	+8.0	115.0	+3.1		
	15:02	2.030	2.035	15.7	17.0			137	132						1665	1561	0.130	-6.0	27.2	-1.3	+8.0	115.0	+3.5		
	15:16	2.030	2.035	28.1	27.0	26.3		125	-	108					1321	1273	0.072	+6.4	28.3	+2.3	-4.0	116.0	-		

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HIGH ALTITUDE

Goat	Collection Period min:sec	$\dot{V}_i$ ml/min	$\dot{V}_o$ ml/min	$[HCO_3^-]$, mM/L c_i	c_o	c_p	cist CSF	$[Cl^-]$, mM/L c_i	c_o	c_p	cist CSF	[Lactate], mM/L c_o	c whole blood	cist CSF	Inulin cpm/ml c_i	c_o	CIn ml/min	HCO_3^- c_i-c_{csf} mM/kg H_2O	c_p mM/kg H_2O	Flux µM min	Cl^- c_i-c_{csf} mM/L	c_p mM/kg H_2O	Flux µM min	Lactate c_p mM/kg H_2O	Flux µM min
RU	-	1.732	-	21.9	-	-	20.8	-	-	-	129.5	-		3.98	864	-	-	+1.1	-	-	-	-	-	-	-
	-	1.732	-	21.9	-			-	-			-					-	+1.1	-	-	-	-	-	-	-
	20:11	1.732	1.813	15.4	16.2	21.9		137	134	110.8		1.45	0.9		880	768	0.172	-5.4	25.5	+0.5	+7.5	119.1	+1.4	1.10	-1.7
	16:14	1.732	1.656	15.4	16.3			137	133.5			1.33				760	0.350	-5.4	25.5	+0.4	+7.5	119.1	+2.1	1.10	-
	18:50	1.732	2.020	29.5	25.0	20.7		120	-	113.1		2.28	1.2		1110	732	0.600	+8.7	22.3	+5.3	-9.5	121.6	-	1.20	-2.8
AC	18:06	1.743	1.719	24.0	21.9	21.6	19.9	128	127.5	110.7	130.4	1.95	1.1	4.32	882	770	0.277	+4.1	23.2	+2.6	-2.4	121.2	-0.9	1.30	-1.30
	15:18	1.743	1.882	24.0	21.8			128	127			1.64				738	0.201	+4.1	23.2	+4.3	-2.4	121.2	-0.2	1.30	-0.71
	15:04	1.743	1.912	15.6	17.1	21.4		136	132	112.6		1.66	0.9		988	774	0.312	-4.3	23.0	+1.5	+5.6	122.8	+2.6	1.12	-1.20
	15:02	1.743	1.950	15.6	16.5			136	132.5			1.60				802	0.204	-4.3	23.0	+1.1	+5.6	122.8	+2.1	1.12	-1.03
	21:19	1.743	1.047	28.1	-	20.6		123	-	112.0		1.60	0.8		932	816	0.944	+8.2	22.2	-	-7.4	123.6	-	1.00	-1.19
	-		-	-	-				-									+8.2	22.2	-	-7.4	123.6	-	1.00	-
NU	15:03	1.729	1.902	24.7	21.5	21.7	19.7	127	-	112.7	128.8	1.34	0.72	3.94	1058	720	0.638	+5.0	23.3	+7.0	-	121.2	-	0.90	-1.12
	15:03	1.729	1.901	24.7	21.5			127	-			1.64				736	0.585	+5.0	23.3	+6.9	-	121.2	-	0.90	-1.84
	15:09	1.729	1.800	17.6	-	20.5		135	131	114.0		1.68	0.80		1074	792	0.545	-2.1	22.0	-	+6.0	122.7	+1.8	0.99	-1.54
	15:04	1.729	1.744	17.6	-			135	-			1.41				778	0.642	-2.1	22.0	-	-	122.7	-	0.99	-1.00
	13:58	1.729	1.246	28.1	23.5	21.7		124	-	115.0		2.36	0.76		954	754	0.941	+8.4	23.3	+7.9	-	123.6	-	0.95	-3.08
	12:32	1.729	0.769	28.1	23.6			124	-			2.17				768	1.378	+8.4	23.3	+7.6	-	123.6	-	0.95	-2.62
SO	15:05	2.040	2.049	22.5	20.9	21.1	18.4	130	130	111.5	132.0	-	0.59	4.46	1283	1197	0.138	+4.1	22.7	+3.5	-2.0	119.9	-1.5	0.72	-
	15:00	2.040	2.127	22.5	20.8			130	130			1.39				1203	0.050	+4.1	22.7	+3.7	-2.0	119.9	-1.4	0.72	-1.50
	15:20	2.040	2.080	15.2	15.3	20.2		136.5	134.5	111.0		-	0.80		1189	1145	0.040	-3.2	21.7	+0.3	+6.5	119.4	+2.9	1.00	-
	15:10	2.040	2.097	15.2	-			136.5	134.5			1.33				1175	0.033	-3.2	21.7	-	+6.5	119.4	+2.7	1.00	-0.70
	15:08	2.040	1.989	27.4	24.2	18.8		124	-	111.0		1.305	0.80		1097	1087	0.070	+9.0	20.2	+6.4	-8.0	119.4	-	1.00	-0.63
	14:57	2.040	1.649	27.4	24.5			124	-			1.48				1058	0.466	+9.0	20.2	+5.5	-8.0	119.4	-	1.00	-1.02
TU	14:41	2.033	2.009	20.3	-	20.6	18.5	130	129.5	109.0	130.0			4.47	646	618	0.115	+1.8	22.1	-	0.0	117.2	-0.1		
	14:55	2.033	1.996	20.3	19.1			130	129							588	0.238	+1.8	22.1	+3.0	0.0	117.2	-0.3		
	14:49	2.033	2.014	14.3	-	19.6		137.5	-	111.0					638	-	-	-4.2	21.0	-	+7.5	119.4	-		
	14:30	2.033	1.973	14.3	14.25			137.5	135							612	0.145	-4.2	21.0	+0.7	+7.5	119.4	+3.75		
	14:57	2.033	2.045	26.3	23.5	18.8		124	-	111.0					619	570	0.163	+7.8	20.2	+5.1	-6.0	119.4	-		
	15:03	2.033	2.047	26.3	-			124	-							577	0.134	+7.8	20.2	-	-6.0	119.4	-		
LI	14:31	2.036	1.832	23.3	-	21.6	20.1	129	128.5	111.0	131.0				1274	1145	0.433	+3.2	23.2	-	-2.0	119.3	-1.1		
	14:50	2.036	1.970	23.3	21.6			129	-							1212	0.170	+3.2	23.2	+3.6	-2.0	119.3	-		
	14:45	2.036	1.830	15.9	16.2	20.65		138	135.5	111.0					1125	1031	0.392	-4.2	22.2	+0.5	+7.0	119.3	+2.1		
	15:04	2.036	1.838	15.9	-			138	135.5							1096	0.252	-4.2	22.2	-	+7.0	119.3	+4.2		
	14:51	2.036	1.872	28.6	26.4	20.5		120	-	111.0					1131	1133	0.160	+8.5	22.0	+4.5	-11.0	119.3	-		
	15:01	2.036	1.871	28.6	-			120	-							1108	0.207	+8.5	22.0	-	-11.0	119.3	-		